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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,416	03/29/2001	David Bar-Or	4172-15-1	5597

22442 7590 06/26/2003

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EXAMINER
SHAHNAN SHAH, KHATOL S

ART UNIT	PAPER NUMBER
1645	20

DATE MAILED: 06/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/820,416	BAR-OR ET AL.	
	Examiner	Art Unit	
	Khatol S Shahnan-Shah	1645	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 June 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached response*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *48-53,56-58,60-61,63-64 and 66-68*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Attachment to Advisory Action

1. The reply filed 6/6/2003 under 37 CFR 1.116 in reply to the final rejection has been entered, but is not deemed to place the application in condition for allowance.

For purposes of appeal, the status of the claims is as follows:

Allowed claim(s): None

Rejected claim(s): 48-53,56-58,60-61,63-64 and 66-68

Claim(s) objected to: None

Restriction Requirement

2. Applicants comments in regard to claim 55 reading on the elected species cobalt is noted. Claim 55 refers to other ions on Groups 1b-7b or 8 of the Periodic Table of the elements not only cobalt.

Rejections Maintained

3. Rejection of claims 48, 49, 50-53, 56-58, 60-61, 63-64 and 66- 68 under 35 103 (a) made in paragraph 9 of the office action mailed July 02, 2002, paper # 13 is maintained.

The rejection was as stated below:

Claims 48, 49, 50-53, 56-58, 60-61, 63-64 and 66- 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bar-Or et al. (US Patent No: 5,227,307) in view of Crapo et al. (US Patent No. 5,994,339) and further in view of Young et al. (6,375,930).

Claims are drawn to a method of monitoring or assessing treatment of a disease or condition with a compound that produces free radicals comprising:

a) obtaining a biological sample;

b) treating the patient with a compound;

c) obtaining additional biological samples after treatment; and determining the change of albumin in the sample by:

d) contacting each of the biological sample with excess quantity of a metal ion salt;

e) determing the amount of bound metal ion to the albumin;

f) determing if there is a change in the amount of bound metal ion.

Bar-Or et al. (US Patent No: 5,227,307) teach a method of monitoring disease or condition in a patient that produces free radicals comprising:

a) obtaining a biological sample and determining the change of albumin in the sample by:

b) contacting each of the biological samples with excess quantity of a metal ion salt;

c) determing the amount of bound metal ion to the albumin;

d) determing if there is a change in the amount of bound metal ion.

(see abstract and claims).

Bar-Or et al. teach a method for detecting ischemic states (lack of oxygen) in a patient by contacting a sample of serum with a metal ion capable of binding to metal binding sites in the sample to form a mixture and then detecting the presence of unbound metal ion to determine the ischemic event (see example 1 and claims). Furthermore, the prior art teaches that several methods could be used to measure the metal ion binding to the albumin such as atomic absorption, atomic emission spectroscopy and determing the color intensity by spectrophotometer (see column 3, lines 44-54). Bar-Or et al. teach a variety of metal ion salts including cobalt (see column 5, lines 23-40). Bar-Or et al. teach that the quantity of free metal

ions in the sample may also be detected by colorimetric means and teach a variety of color forming compounds (see column 6, lines 20-65). Bar-Or et al. (US Patent No: 5,290,519) teach a method of quantifying modified albumin, column 3, lines 14-22 recite that " In the present method, a sample of serum, plasma, fluid or tissue from a patient is reached with metal ions, generally in the form of an aqueous salt solution, so that the metal ion become bound to the metal binding sites on the protein in the sample. Metal ions bind to the proteins containing metal ion- binding sites such as thiol, hydroxy, carboxy, amino groups present on the amino acids which constitute the protein." Therefore, Bar-Or et al. teach modified protein (i.e. modified albumin) since metal binding capacity is reduced or inhibited in the albumin. Bar-Or et al. do not teach treating patient with a compound or superoxide dismutase as a free radical scavenger. However, Crapo et al. teach treating patient with an effective amount of a mimetic of superoxide dismutase as a free radical scavenger (see column 1, background, column 2, summary of invention and claims specially claim 1). Crapo et al. do not teach photosensitizing agents and porfimer sodium. However, Young et al. teach photodynamic therapy and porfimer sodium (see column 3, lines 10-20 and column 4, lines 50-56). It would have *prima facie* obvious to a person of ordinary skill in art at the time the invention was made to use and combine the methods set forth in Bar-Or et al., Crapo et al. and Young et al. to obtain the claimed invention. One of ordinary skill in art would have been motivated with the reasonable expectation of success to develop a method of monitoring or assessing treatment of a disease by detecting or quantifying free radical damage as taught by Bar-Or et al. absent any convincing evidence to the contrary.

Applicants' arguments filed June 6, 2003 have been fully considered but they are not persuasive.

Applicants argue that Bar-Or et al. is directed to the diagnosis of one special condition – ischemia. Bar-Or et al. do not teach or suggest monitoring or assessing the effectiveness of treatment of patients with drugs that produce or reduce free radicals. Applicants further argue that the language of lines 23-25 of column 2 of Bar-Or et al. is referred to rehabilitative treatments for ischemia, such as angioplasty and the statement can not be interpreted to mean any other kind of treatment. Applicants further argue that this general language does not provide any motivation to combine the teachings of Bar-Or et al. and Crapo et al. and Young et al.

It is the examiner's position that Bar-Or et al. teach or suggest monitoring or assessing the effectiveness of treatment of patients for example in column 2, lines 23-25 Bar-Or et al. recite " A further object of the invention is to provide a method for evaluating rehabilitated patients suffering from ischemia (myocardial infraction) to determine circulatory effectiveness", in column 9 lines 34-41 Bar-Or et al. recite " The results indicate that the present method can be used to detect ischemic states. The present method is effective in distinguishing between ischemic cardiogenic chest pain and non-cardiogenic chest pain. Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced other than as specifically described herein".

It is also the examiner's position that claims are drawn to a method of monitoring or assessing treatment of a disease or condition that produces free radicals. Ischemia is a disease or condition, which is frequently caused by arterial vessel disease. One feature of arterial vessel disease is the progression from the atheromatous state to the sclerotic state in which large quantities of calcium enter the aterial musculature. The intracellular calcium activates the

protease calpain, which converts xanthine dehydrogensase to xanthine oxidase. Xanthine oxidase acts on xanthine and hypoxanthine to form free radical (see Bar-Or et al. column lines 40-51). The instant specification in the paragraph bridging pages 12 and 13 recites, " The methods of the invention can be used to monitor and assess disease and conditions in which free radicals play a role." The paragraph further recites ischemia as one of these conditions (see page 13, line 4). Therefore, the invention is obvious over Bar-Or et al. in view of Crapo et al. and further in view of Young et al.

Conclusion

4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is (703) 308-8896. The examiner can normally be reached on 7:30 AM - 4 PM from Monday through Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette F Smith, can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned to is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Khatol Shahnan-Shah, BS, Pharm, MS

Biotechnology Patent Examiner

Art Unit 1645

June 20, 2003

RODNEY P SWARTZ, PH.D
PRIMARY EXAMINER